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(54) Title: **NOVEL PREPARATION AND ADMINISTRATION FORM COMPRISING AN ACID-LABILE ACTIVE COMPOUND**

(57) Abstract: Novel administration forms and preparations for acid-labile active compounds are described. The novel administration forms contain individual active compound units, the active compound being present in the active compound units in a matrix made of a mixture comprising at least one fatty alcohol and at least one solid paraffin, in a matrix made of a mixture of a triglyceride and at least one solid paraffin or in a matrix made of a mixture comprising at least one fatty acid ester and at least one solid paraffin. In particular, the active compound units are microspheres which can be produced by prilling.

Novel preparation and administration form comprising an acid-labile active compound**Technical field**

The present invention relates to the field of pharmaceutical technology and describes a novel administration form comprising an acid-labile active compound, in particular an acid-labile proton pump inhibitor. Furthermore, the invention also relates to processes for the production of the administration form, preparations which can be used for the production of the administration form, and a process for the production of the preparations.

Prior art

It is generally known to coat peroral administration forms, e.g. tablets or pellets which contain an acid-labile active compound, with an enteric coating which, after passage through the stomach, rapidly dissolves in the alkaline medium of the intestine. Examples of such acid-labile active compounds are acid-labile proton pump inhibitors (H^+/K^+ ATPase inhibitors), in particular pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, such as are disclosed, for example, in EP-A-0 005 129, EP-A-0 166 287, EP-A-0 174 726 and EP-A-0 268 956. On account of their H^+/K^+ ATPase-inhibiting action, these are of importance in the therapy of diseases which are due to increased gastric acid secretion. Examples of active compounds from this group which are already commercially available are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: lansoprazole) and 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulfinyl]-1H-benzimidazole (INN: rabeprazole).

Because of their strong tendency to decompose in a neutral and, in particular, in an acidic environment, where strongly colored decomposition products are also formed, for oral preparations it is also necessary in this case to protect the active compounds from the action of acids. In the case of the strongly acid-labile pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, it is moreover necessary to process these in the tablet core or in pellets in the form of their alkaline salts, for example as sodium salts, or together with alkaline substances. Since the substances suitable for enteric coatings are those having free carboxyl groups, the problem results that the enteric coating is partly dissolved or even dissolved from inside because of the alkaline medium in the interior and the free carboxyl groups promote the decomposition of the active compounds. It is therefore necessary to provide an isolating intermediate layer (subcoating) between the enteric coating and the alkaline tablet core or pellet. It is proposed in EP-A-0 244 380 to coat cores which contain the active compound together with alkaline compounds or

as an alkaline salt with at least one layer of nonacidic, inert pharmaceutically acceptable substances, which are soluble in water or rapidly decompose in water, before the enteric layer is applied. The intermediate layer or intermediate layers act as pH-buffering zones in which the hydrogen ions diffusing in from outside can react with the hydroxyl ions diffusing from the alkaline core. In order to increase the buffer capacity of the intermediate layer, it is proposed to incorporate buffer substances into the intermediate layer(s). In practice, it is possible by this process to obtain somewhat stable preparations. However, relatively thick intermediate layers are needed in order to avoid the unsightly discolorations occurring even in the case of only slight decomposition. Moreover, a considerable effort is to be made in the preparation to avoid traces of moisture.

In EP-A-0 519 365, a formulation on the principle of the alkaline core coated with a water-soluble intermediate layer and an enteric coating is proposed for the active compound pantoprazole, in which improved stability is achieved by use of polyvinylpyrrolidone and/or hydroxypropylmethylcellulose as binders for the alkaline core.

EP-A-0 342 522 discloses a formulation for acid-sensitive benzimidazoles in which, between the alkaline core and the enteric coating, an intermediate layer is located which is composed of only slightly water-soluble film-forming material, such as ethylcellulose and polyvinyl acetate, and a slightly water-soluble finely granular inorganic or organic material suspended therein, such as, for example, magnesium oxide, silicon oxide or sucrose fatty acid esters.

EP-A-0 277 741 describes spherical granules having a core which is coated with spray powder, which contains low-substituted hydroxypropylcellulose and a benzimidazole compound having anti-ulcer activity. These granules can be coated with an enteric coating agent.

WO 96/01623, WO 96/01624 and WO 96/01625 describe an administration form for acid-labile H^+/K^+ ATPase inhibitors, in which the active compound pellets are compressed together with tablet excipients to give a tablet. The pellets consist of cores which contain the acid-labile- H^+/K^+ ATPase inhibitor together with alkaline compounds or as an alkaline salt. The cores of the pellets are coated with one or more layers, at least one layer having enteric properties. In a mechanical respect, the enteric coating must in this case be constituted such that on compression to give tablets the acid resistance of the pellets is not adversely affected. It is mentioned that the production of the cores of the pellets can be carried out by spray drying.

WO 97/25030 describes the processing of the abovementioned pellets to give an effervescent tablet.

WO 98/52564 describes a pharmaceutical composition in pellet form, which has an inert core, a benzimidazole on or in the core, a moisture-resistant layer around the core and an enteric coating over

the moisture-resistant layer. Hydrophobic materials such as, for example, cetyl alcohol are mentioned as constituents of the moisture-resistant layer.

EP-A-0 514 008 describes pharmaceutical administration forms for acid-labile benzimidazoles based on a solid matrix of a polyglycerol fatty acid ester or a lipid and the active compound. At least in the vicinity of the matrix surface, a substance is dispersed which develops viscosity on contact with water. It is mentioned that such an administration form can settle in the digestive tract, remains there for a relatively long time and the bioavailability of the active compound is increased.

As the abovementioned prior art shows, the production of peroral administration forms for acid-labile active compounds requires technically complicated processes.

Description of the invention

It is the object of the present invention to provide a novel administration form for acid-labile active compounds, which can be prepared without great technical effort and exhibits good controllability of the release of active compound. A further object of the invention is the provision of an administration form in which the acid-labile active compound does not have to be protected by an enteric coating.

It has now surprisingly been found that this object can be achieved by an administration form which contains multiple individual active compound units, the acid-labile active compound being present in the individual active compound units in a matrix made of a mixture of at least one fatty alcohol and at least one solid paraffin, being present in a matrix made of a mixture of at least one triglyceride and at least one solid paraffin or being present in a matrix made of a mixture of at least one fatty acid ester and at least one solid paraffin.

One subject of the invention is therefore an administration form for acid-labile active compounds, comprising pharmaceutical excipients and multiple individual active compound units, wherein the acid-labile active compound is present in the individual active compound units in a matrix made of a mixture comprising at least one fatty alcohol and at least one solid paraffin.

A further subject of the invention is also an administration form for acid-labile active compounds, comprising pharmaceutical excipients and multiple individual active compound units, wherein the acid-labile active compound is present in the individual active compound units in a matrix made of a mixture comprising at least one triglyceride and at least one solid paraffin.

The invention furthermore relates to an administration form for acid-labile active compounds, comprising pharmaceutical excipients and multiple individual active compound units, wherein the acid-labile active compound is present in the individual active compound units in a matrix made of a mixture comprising at least one fatty acid ester and at least one solid paraffin.

Further subjects follow from the patent claims.

The multiple individual active compound units (also described as preparations below) within the meaning of the invention are multiple individual units, in which at least one active compound particle is present in a matrix made of a mixture comprising at least one fatty alcohol and at least one solid paraffin, in a matrix made of a mixture comprising at least one triglyceride and at least one solid paraffin or in a matrix made of a mixture comprising at least one fatty acid ester and at least one solid paraffin. Preferably, the active compound units are microspheres.

The active compound units according to the invention are distinguished in particular by good stability, release of the active compound which can be controlled by means of the particle size, good flow behavior, good compressibility and by a constant (determined by the uniform surface) release of active compound.

The particle size of the individual units is advantageously less than or equal to 2 mm, preferably from 50-800 μm , particularly preferably 50-700 μm and very particularly preferably 50-600 μm . They are preferably microspheres having a particle size of 50-500 μm , particularly preferably of 50-400 μm . They are particularly preferably monomodal microspheres having a particle size of 50-400 μm , particularly preferably of 50-200 μm .

Acid-labile active compounds within the meaning of the present invention are, for example, acid-labile proton pump inhibitors.

Acid-labile proton pump inhibitors (H^+/K^+ ATPase inhibitors) within the meaning of the present invention which may be mentioned are in particular substituted pyridin-2-yl-methylsulfinyl-1H-benzimidazoles, such as are disclosed, for example, in EP-A-0 005 129, EP-A-0 166 287, EP-A 0 174 726, EP-A-0 184 322, EP-A-0 261 478 and EP-A-0 268 956. Mention may preferably be made here of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: lansoprazole) and 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulfinyl]-1H-benzimidazole (INN: rabeprazole).

Further acid-labile proton pump inhibitors, for example substituted phenylmethanesulfinyl-1H-benzimidazoles, cycloheptapyridin-9-ylsulfinyl-1H-benzimidazoles or pyridin-2-ylmethanesulfinylthienimidazoles, are disclosed in DE-A-35 31 487, EP-A-0 434 999 and EP-A-0 234 485. Examples which may be mentioned are 2-[2-(N-isobutyl-N-methylamino)benzylsulfinyl]benzimidazole (INN: leminoprazole) and 2-(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ylsulfinyl)-1H-benzimidazole (INN: nepaprazole).

The acid-labile proton pump inhibitors are chiral compounds. The term acid-labile proton pump inhibitor also includes the pure enantiomers of the acid-labile proton pump inhibitors and their mixtures in any mixing ratio. Pure enantiomers which may be mentioned by way of example are 5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (INN: esomeprazole) and (-)-pantoprazole.

The acid-labile proton pump inhibitors are present here as such or preferably in the form of their salts with bases. Examples of salts with bases which may be mentioned are sodium, potassium, magnesium and calcium salts. If desired, the salts of the acid-labile proton pump inhibitors with bases can also be present in hydrate form. Such a hydrate of the salt of an acid-labile proton pump inhibitor with a base is disclosed, for example, in WO 91/19710.

Particularly preferred acid-labile proton pump inhibitors which may be mentioned are pantoprazole sodium sesquihydrate (= pantoprazole sodium x 1.5 H₂O), (-)-pantoprazole sodium sesquihydrate, omeprazole magnesium, omeprazole, esomeprazole magnesium and esomeprazole.

The fatty alcohol is preferably a linear, saturated or unsaturated primary alcohol having 10-30 carbon atoms. It is preferably a primary alcohol having 10 to 18 carbon atoms in linear chains. Fatty alcohols which may be mentioned by way of example are cetyl alcohol, myristyl alcohol, lauryl alcohol or stearyl alcohol, cetyl alcohol being preferred. If desired, mixtures of fatty alcohols can also be present.

The triglyceride is glycerol whose three hydroxyl groups are esterified by carboxylic acids. Preferably, the carboxylic acids are monobasic carboxylic acids having 8 to 22 carbon atoms, preferably naturally occurring carboxylic acids. In this context, they can be different or, preferably, identical carboxylic acids. Examples which may be mentioned are tristearate, tripalmitate and particularly preferably trimyristate (these triglycerides are commercially available under the name Dynasan 118, 116 or 114). If desired, mixtures of triglycerides can also be present.

The fatty acid ester is the ester of an alcohol with a fatty acid. In this case, the alcohol is preferably a linear, saturated or unsaturated primary alcohol having 10-30, preferably having 12 to 18, carbon atoms. The fatty acid is preferably a monobasic carboxylic acid having 8 to 22, in particular 12 to 18,

carbon atoms, preferably a naturally occurring carboxylic acid. According to the invention, preferred fatty acid esters are those having a melting point of greater than 30°C. A fatty acid ester which may be mentioned by way of example is cetyl palmitate, which is commercially available, for example, under the name Cutina® CP. If desired, mixtures of fatty acid esters can also be present.

The solid paraffin is preferably paraffinum solidum (paraffin wax). Alternatively, for example, ozocerite can also be used. If desired, mixtures can also be used.

If desired, the mixtures in the individual active compound units can have one or more further pharmaceutically suitable excipients. Examples of further suitable excipients which may be mentioned are polymers, sterols and basic compounds.

Examples of polymers which may be mentioned are povidone (e.g. Kollidon® 17, 30 and 90 from BASF), vinylpyrrolidone/vinyl acetate copolymer and polyvinyl acetate. Mention may furthermore be made of cellulose ethers [such as, for example methylcellulose, ethylcellulose (Ethocel®) and hydroxypropylmethylcellulose], cellulose esters [such as cellulose acetate phthalate (CAP), cellulose acetate/trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HP50 and HP55) or hydroxypropylmethylcellulose acetate succinate (HPMCAS)], methacrylic acid/methyl methacrylate copolymer or methacrylic acid/ethyl methacrylate copolymer (Eudragit® L). The polymer is preferably povidone or ethylcellulose. If desired, mixtures of polymers can also be present. By addition of suitable polymers, it is possible, for example, to influence the properties of the individual active compound units pharmaceutically (e.g. release of the active compound). By addition of suitable polymers such as cellulose acetate phthalate and hydroxypropylmethylcellulose phthalate (HP50 and HP55), a gastric juice resistance (delayed release according to definition of United States Pharmacopeia) of the individual active compound units can be achieved. For the production of an active compound unit having controlled release (extended release according to definition of United States Pharmacopeia) of the active compound, it is possible to add suitable polymers such as ethylcellulose and cellulose acetate.

The sterol is preferably a phytosterol or a zoosterol. Examples of phytosterols which may be mentioned are ergosterol, stigmasterol, sitoisterol, brassicasterol and campesterol. Examples of zoosterols which may be mentioned are cholesterol and lanosterol. If desired, mixtures of sterols can also be present.

Suitable basic compounds are, for example, inorganic basic salts such as ammonium carbonate and sodium carbonate, amines such as meglumine, di- or triethylamine and TRIS (2-amino-2-hydroxymethyl-1,3-propandiol) or fatty amines such as stearylamine. Stearylamine may be preferably mentioned. By the addition of basic compounds to the mixtures in the individual units, particularly stable preparations are obtained and possible discolorations are avoided.

The proportion (in percent by weight) of active compound in the individual active compound unit is advantageously 1-90%. The proportion of active compound is preferably 2-70%, particularly preferably 5-40%, in particular 10-20%. The proportion of fatty alcohol in the individual active compound unit is advantageously 10-70%, preferably 20-70%, particularly preferably 20-60% and in particular 30-60%. The proportion of triglyceride in the individual active compound unit is advantageously 10-70%, preferably 20-70%, particularly preferably 20-60% and in particular 30-60%. The proportion of fatty acid ester in the individual active compound unit is advantageously 10-70%, preferably 20-70%, particularly preferably 20-60% and in particular 30-60%. The proportion of solid paraffin is advantageously 10-70%, preferably 20-60% and in particular 30-60%. If present, the proportion of polymer in the individual active compound unit is expediently 1-25%, preferably 1-10%, particularly preferably 5-10%. If present, the proportion of sterol is expediently 1-10%, preferably 1-5%. If present, the proportion of basic compound is 0.05-5%, preferably 0.1-1%.

Preferred individual active compound units according to the invention consist of 2-70% of active compound, 10-60% of fatty alcohol, 10-60% of solid paraffin, 1-15% of polymer and 0.1-2% of a basic compound. Further preferred individual active compound units according to the invention consist of 2-70% of active compound, 10-60% of triglyceride, 10-60% of solid paraffin, 1-15% of polymer and 0.1-2% of a basic compound. Other preferred individual active compound units according to the invention consist of 2-70% of active compound, 10-60% of fatty acid ester, 10-60% of solid paraffin, 1-15% of polymer and 0.1-2% of a basic compound.

Particularly preferred individual active compound units according to the invention consist of 5-40% of active compound, 20-60% of fatty alcohol, 10-60% of solid paraffin, 1-15% of polymer and 0.1-1% of a basic compound. Further particularly preferred individual active compound units according to the invention consist of 5-40% of active compound, 20-60% of triglyceride, 10-60% of solid paraffin, 1-15% of polymer and 0.1-1% of a basic compound. Other particularly preferred individual active compound units according to the invention consists of 5-40% of active compound, 20-60% of fatty acid ester, 10-60% of solid paraffin, 1-15% of polymer and 0.1-1% of a basic compound.

Examples of active compound units according to the invention contain 5-40% of pantoprazole sodium sesquihydrate, 10-40% of cetyl alcohol, 5-60% of solid paraffin, 1-5% of polymer and 0.1-0.2% of a basic compound. Further examples of active compound units according to the invention contain 5-40% of pantoprazole sodium sesquihydrate, 10-40% of glyceryl tripalmitates, 5-60% of solid paraffin, 1-5% of polymer and 0.1-0.2% of a basic compound. Still other examples of active compound units according to the invention contain 10-20% of pantoprazole sodium sesquihydrate, 20-40% of triglyceride, 40-70% of solid paraffin, 1-5% of sterol and 0.05-0.1% of a basic compound.

The individual active compound units can be prepared, for example, by spray drying or preferably by spray solidification, in particular also by spray prilling. The preparation is particularly preferably carried out by prilling, in particular by vibration prilling. Spray drying is carried out from a suitable solvent. Suitable solvents for spray drying are preferably those in which the fatty alcohol, the triglyceride or the fatty acid ester and the solid paraffin are soluble, while the active compound is insoluble. The suitable solvents can also be solvent mixtures.

If the active compound employed is an acid-labile proton pump inhibitor, in particular a substituted pyridin-2-ylmethylsulfinyl-1H-benzimidazole, the suitable solvents are, for example, hydrocarbons, chlorinated hydrocarbons and ethyl acetate. Hydrocarbons which can be mentioned are in particular linear or branched alkanes or alternatively cycloalkanes. Examples of linear alkanes are pentane, hexane and heptane. Examples of branched alkanes which may be mentioned are 2-methylpentane and 3-methylpentane. Examples of cycloalkanes which may be mentioned are cyclohexane and cyclopentane. If desired, mixtures of the hydrocarbons such as, for example, petroleum ether can also be employed. A chlorinated hydrocarbon which may be mentioned is chloroform or, preferably, dichloromethane.

For spray drying, the fatty alcohol, the triglyceride or the fatty acid ester and the solid paraffin, and, if desired, the further pharmaceutical constituents are dissolved in the suitable solvent and the active compound is suspended therein. If desired, the active compound can also be suspended and the fatty alcohol, the triglyceride or the fatty acid ester and the solid paraffin can then be dissolved. The particle size of the active compound employed should in this case advantageously be less than 40 μm . The suspension obtained is then sprayed in a spray dryer.

Spray drying is carried out in a manner known per se. A detailed presentation of this technique is found in K. Masters, *Spray Drying Handbook*, 5th Ed. 1991, and J. Broadhead, S.K. Edmond Ronan, C. T. Rhodes, *The Spray Drying of Pharmaceuticals*, *Drug Dev. Ind. Pharm.* 18, 1169 (1992). The principle of spray drying consists in splitting up a solution or suspension of the product to be dried into fine droplets and drying it with a hot stream of gas. The solid component remaining after evaporation of the solvent is removed from the stream of gas by means of a cyclone and/or by a filter unit and collected.

Suitable drying gases are, in particular, air and preferably nitrogen. The gas inlet temperature depends on the solvent.

The invention further relates to a preparation comprising an acid-labile active compound, at least one fatty alcohol or at least one triglyceride or at least one fatty acid ester and at least one solid paraffin,

obtainable by spray drying a suspension of the acid-labile active compound in a solution of the fatty alcohol, the triglyceride or the fatty acid ester and the solid paraffin in a suitable solvent.

The preparation of the individual active compound units is preferably carried out by spray solidification or by prilling, the preparation very particularly preferably being carried out by vibration prilling.

For spray solidification or prilling, the fatty alcohol, the triglyceride or the fatty acid ester is expediently liquefied to give a clear melt together with the solid paraffin and, if desired, further excipients. The active compound is dissolved or dispersed in this solution and the solution or dispersion obtained is sprayed or preferably prilled in a suitable device. A dispersion of the active compound in a melt of the excipients is preferably used.

Spray solidification is carried out in a manner known per se. A detailed presentation of this technique is found in P.B. Deasy, Microencapsulation and Related Drug Process (1984).

The preparation of the individual active compound units is particularly preferably carried out by solidification from the liquid phase by production of droplets by means of vibrating nozzles and by solidification of the droplets formed after stabilization thereof by drying or cooling in a suitable medium (preferably gaseous or liquid). The suitable medium can be, for example, cooled gas such as air or nitrogen. Such a process is disclosed, for example, in DE 27 25 924. The phase flowing to the nozzle is particularly preferably kept at a constant temperature here. Solidification is preferably carried out by means of sudden quenching in a suitable cooling medium. In the prilling, the liquid phase flowing to the nozzle, the vibrating nozzle and the drops formed by prilling are preferably kept, until the stabilization of their spherical form, at a constant temperature which is 1°C to 10°C above the melting temperature of the liquid phase, and the solidification of the drops after stabilization thereof is carried out suddenly by quenching using a gaseous or liquid cooling medium, whose operating temperature is at least 30°C below the melting temperature of the liquid phase. Such a process and a device suitable for carrying out this process are described, for example, in EP 0 467 221 B1. For prilling by means of vibrating nozzles, suitable units are marketed, for example, by Brace GmbH, Alzenau, Germany. With the aid of prilling by means of vibrating nozzles, the individual active compound units can be obtained in the form of microspheres having a narrow monomodal particle spectrum in the particle size range from 50 µm to 2 mm. Owing to the narrow monomodal particle spectrum and a uniform, spherical form of the microspheres thus obtained, a uniformly smooth surface, a uniform, defined delivery of active compound and, with respect to the gastric passage in the case of oral administration forms (determined by the small particles), behavior like that of a solution is to be expected. The individual active compound units according to the invention thus differ from active compound-containing pellets obtained by extrusion.

In a further aspect, the invention therefore relates to microspheres comprising an acid-labile active compound and pharmaceutically acceptable excipients. The microspheres are preferably monomodal microspheres having a particle size range of 50-800 μm , preferably 50-500 μm , particularly preferably 50-400 μm , in particular of 50-200 μm . The microspheres preferably contain an acid-labile proton pump inhibitor.

The invention further relates also to microspheres comprising an acid-labile active compound and at least one fatty alcohol as a pharmaceutically acceptable excipient. In addition to the fatty alcohol, the microsphere can contain one or more further pharmaceutically suitable excipients. Examples of further suitable excipients which may be mentioned are polymers, sterols and basic compounds, the terms polymers, sterols and basic compounds having the above-mentioned meanings. In this case, the proportion (in percent by weight) of active compound in the individual active compound unit is advantageously 1-90%. The proportion of active compound is preferably 2-70%, particularly preferably 5-40%, in particular 10-20%. The proportion of fatty alcohol in the individual active compound unit is preferably 10-90%, preferably 30-85%, particularly preferably 60-80%. If present, the proportion of polymer in the individual active compound unit is expediently 1-25%, preferably 1-10%, particularly preferably 5-10%. If present, the proportion of sterol is expediently 1-10%, preferably 1-5%. If present, the proportion of basic compound is preferably 0.05-5%, preferably 0.1-1%.

They are particularly preferably microspheres obtainable by production of drops of a solution or dispersion of the acid-labile active compound in at least one fatty alcohol by means of vibrating nozzles and by solidification of the drops formed after stabilization thereof in a suitable medium. Preferably, the solution or dispersion flowing to the nozzle is kept at constant temperature.

The invention further relates to microspheres obtainable by production of drops of a solution or dispersion of the acid-labile active compound in at least one fatty alcohol, triglyceride or fatty acid ester together with at least one solid paraffin by means of vibrating nozzles and by solidification of the drops formed after stabilization thereof by cooling in a suitable medium. Preferably, the solution or dispersion flowing to the nozzle is kept at constant temperature.

The particle size of the active compound employed in the spray drying or spray solidification, prilling or vibration prilling is advantageously less than or equal to 100 μm , in particular less than 40 μm . The particle size is preferably in the range from 1-20 μm , particularly preferably in the range from 3-15 μm . Such a particle size can be achieved, for example, by grinding the active compound in a suitable mill.

The individual active compound units (preparations) according to the invention can then be used as a basis for the production of the administration forms according to the invention. Administration forms according to the invention which may be mentioned, to which the preparations can be processed, are,

for example, suspensions, gels, tablets, coated tablets, multicomponent tablets, effervescent tablets, rapidly disintegrating tablets, powders in sachets, sugar-coated tablets, capsules or alternatively suppositories. Preferred administration forms here are peroral administration forms. Rapidly disintegrating tablets and effervescent tablets are particularly preferred. The excipients which are suitable for the desired administration forms are familiar to the person skilled in the art on the basis of his/her expert knowledge. In the case of peroral administration forms, it is surprisingly possible to dispense with the enteric coating.

The administration forms according to the invention contain the acid-labile active compound in the dose customary for the treatment of the respective disease. The acid-labile proton pump inhibitors according to the invention can be employed for the treatment and prevention of all the diseases which are regarded as treatable or avoidable by the use of pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. In particular, such administration forms according to the invention can be employed in the treatment of stomach disorders. Such administration forms according to the invention contain between 1 and 500 mg, preferably between 5 and 60 mg, of an acid-labile proton pump inhibitor. Examples which may be mentioned are tablets or capsules which contain 10, 20, 40 or 50 mg of pantoprazole. The administration of the daily dose (e.g. 40 mg of active compound) can be carried out, for example, in the form of an individual dose or by means of a number of doses of the administration forms according to the invention (e.g. 2 times 20 mg of active compound).

The administration forms according to the invention can be combined with other medicaments, either in various combinations or in a fixed combination. In connection with the administration forms according to the invention which contain acid-labile proton pump inhibitors as active compounds, combinations with antimicrobial active compounds and combinations with NSAIDs (nonsteroidal antiinflammatory drugs) are worthy of mention. Combination with antimicrobial agents, such as are employed for the control of the microorganism *Helicobacter pylori* (*H. pylori*), may particularly be mentioned.

Examples of suitable antimicrobial active compounds (active against *Helicobacter pylori*) are described in EP-A-0 282 131. Examples of antimicrobial agents suitable for the control of the microorganism *Helicobacter pylori* which may be mentioned are, for example, bismuth salts [e.g. bismuth subcitrate, bismuth subsalicylate, ammonium bismuth(III) potassium citrate dihydroxide, bismuth nitrate oxide, dibismuth tris(tetraoxodialuminate)], but in particular β -lactam antibiotics, for example penicillins (such as benzylpenicillin, phenoxymethylpenicillin, propicillin, azidocillin, dicloxacillin, flucloxacillin, oxacillin, amoxicillin, bacampicillin, ampicillin, mezlocillin, piperacillin or azlocillin), cephalosporins (such as cefadroxil, cefaclor, cefalexin, cefixime, cefuroxime, cefetamet, cefadroxil, ceftibuten, cefpodoxime, cefotetan, cefazolin, cefoperazon, ceftizoxime, cefotaxime, ceftazidime, cefamandol, cefepime, cefoxitin, cefodizime, cefsulodin, ceftriaxone, cefotiam or cefmenoxime) or other β -lactam antibiotics (e.g. aztreonam, loracarbef or meropenem); enzyme inhibitors, for example sulbactam; tetracyclines,

for example tetracycline, oxytetracycline, minocycline or doxycycline; aminoglycosides, for example tobramycin, gentamicin, neomycin, streptomycin, amikacin, netilmicin, paromomycin or spectinomycin; amphenicols, for example chloramphenicol or thiamphenicol; lincomycins and macrolide antibiotics, for example clindamycin, lincomycin, erythromycin, clarithromycin, spiramycin, roxithromycin or azithromycin; polypeptide antibiotics, for example colistin, polymixin B, teicoplanin or vancomycin; gyrase inhibitors, for example norfloxacin, cinoxacin, ciprofloxacin, pefloxacin, fleroxacin or ofloxacin; nitroimidazoles, for example metronidazole; or other antibiotics, for example fosfomycin or fusidic acid. Particularly worthy of mention in this connection is the administration of an acid-labile proton pump inhibitor with the combination of a multiplicity of antimicrobial active compounds, for example with the combination of a bismuth salt and/or tetracyclines with metronidazole or the combination of amoxicillin or clarithromycin with metronidazole and amoxicillin with clarithromycin.

The production of administration forms and preparations according to the invention is described by way of example below. The following examples illustrate the invention in greater detail, without restricting it.

Examples

Production of the preparations

Example 1

50 g of solid paraffin, 34.9 g of cetyl alcohol and 0.1 g of stearylamine are fused to give a clear mixture. 5.0 g of povidone are dissolved in the clear melt. 10.0 g of pantoprazole sodium sesquihydrate are added and homogeneously suspended at a temperature of 56-60°C. The suspension is prilled in the molten state and the drops thus formed are solidified in a cooling zone.

Example 2

55 g of solid paraffin, 30.9 g of cetyl alcohol and 0.1 g of stearylamine are fused to give a clear mixture. 4.0 g of povidone are dissolved in the clear melt. 10.0 g of pantoprazole-magnesium are added and homogeneously suspended at a temperature of 56-60°C. The suspension is prilled in the molten state and the drops thus resulting are solidified in a cooling zone.

Example 3

45.0 g of solid paraffin, 33.8 g of cetyl alcohol, 1.0 g of β -sitosterol and 0.2 g of stearylamine are fused to give a clear mixture. 1.0 g of povidone and 4.0 g of ethylcellulose are dissolved in the clear melt. 15.0 g of pantoprazole sodium sesquihydrate are added and homogeneously suspended at a temperature of 56-60°C. The suspension is prilled in the molten state and the drops thus resulting are solidified in a cooling zone.

Example 4

52.0 g of solid paraffin, 30.3 g of cetyl alcohol and 0.2 g of stearylamine are fused to give a clear mixture. 5.0 g of povidone are dissolved in the clear melt. 12.5 g of pantoprazole sodium sesquihydrate are added and homogeneously suspended at a temperature of 56-60°C. The suspension is prilled in the molten state and the drops thus formed are solidified in a cooling zone.

Example 5

77.2 g of cetyl alcohol and 0.3 g of stearylamine are fused to give a clear mixture. 10.0 g of povidone are dissolved in the clear mixture. 12.5 g of pantoprazole sodium sesquihydrate are added and

homogeneously suspended at a temperature of 56-60°C. The suspension is prilled in the molten state and the drops thus formed are solidified in a cooling zone.

Example 6

47 g of solid paraffin, 40 g of glyceryl tripalmitate (Dynasan 116, Hüls), and 3 g of sitosterol are fused to give a clear mixture at 100°C and cooled to 55-60°C. 10 g of lansoprazole are added and homogeneously suspended. The suspension is added to the feed container of a prilling unit (Brace) and prilled at about 0.1 bar from a 200 µm nozzle. A periodic oscillation of the frequency of about 390 Hz is transmitted to the nozzle head in the course of this. The resulting drops are solidified in a cooling zone using air with a temperature of -30°C.

Example 7

15 g of glyceryl trimyristate (Dynasan 114), 15 grams of glyceryl tripalmitate (Dynasan 116), 50 grams of solid paraffin and 5 g of cholesterol are fused to give a clear mixture at about 100°C. The clear melt is cooled to about 55-65°C. 15 g of rabeprazole are added, the compound is distributed uniformly and the homogeneous suspension is prilled as in Example 6.

Example 8

10 g of glyceryl tripalmitate (Dynasan 116), 20 g of glyceryl trimyristate (Dynasan 114), 52 g of solid paraffin and 3 g of sitosterol are fused to give a clear mixture at about 100°C. The clear melt is cooled to 55-65°C. 15 g of omeprazole Mg are added and homogeneously suspended. The suspension is added to the feed container of a prilling unit (Brace) and prilled at 90 mbar by means of a 200 µm nozzle. A periodic oscillation of the frequency of about 400 Hz is transmitted to the nozzle head in the course of this. The resulting drops are solidified in a cooling zone using air with a temperature of -30°C.

Example 9

18 g of tristearate, 60 g of solid paraffin and 5 g of cholesterol are fused to give a clear mixture. The clear melt is cooled to 56-60°C. 10 g of pantoprazole sodium sesquihydrate are introduced and this is homogeneously dispersed. The suspension is prilled in the molten state in a prilling unit (Brace) having vibrating nozzles and the resulting drops are solidified in a cooling zone.

Example 10

18 g of cetyl palmitate, 40 g of solid paraffin and 2 g of cholesterol are fused to give a clear mixture. The clear melt is cooled to 56-60°C. 10 g of pantoprazole sodium sesquihydrate are introduced and homogenized until a uniform suspension is formed. The liquid suspension is prilled in the molten state in a prilling unit (Brace) having vibrating nozzles and the resulting drops are solidified in a cooling zone.

Example 11

50 g of solid paraffin and 40 g of cetyl palmitate (Cutina® CP) are fused to give a clear mixture at 100°C. The clear melt is cooled to 50-60°C. 10 g of pantoprazole sodium sesquihydrate are introduced and homogeneously suspended. The liquid suspension is prilled in the molten state in a prilling unit (Brace) having vibrating nozzles (200 µm nozzle) and the resulting drops are solidified in a cooling zone.

Example 12

50 g of solid paraffin and 40 g of cetyl alcohol are fused to give a clear mixture at 100°C. The clear melt is cooled to 50-60°C. 10 g of pantoprazole sodium sesquihydrate are introduced and homogeneously suspended. The liquid suspension is prilled in the molten state in a prilling unit (Brace) having vibrating nozzles (200 µm nozzle) and the resulting drops are solidified in a cooling zone.

Example 13

50 g of solid paraffin and 40 g of glyceryl trimyristate are fused to give a clear mixture at 100°C. The clear melt is cooled to 50-60°C. 10 g of pantoprazole sodium sesquihydrate are introduced and homogeneously suspended. The liquid suspension is prilled in the molten state in a prilling unit (Brace) having vibrating nozzles (200 µm nozzle) and the resulting drops are solidified in a cooling zone.

Example 14

47 g of solid paraffin, 40 g of glyceryl tripalmitate (Dynasan 116, Hüls) and 3 g of sitosterol are fused to give a clear mixture at 100°C and cooled to 55-60°C. 10 g of lansoprazole are added and homogeneously suspended. The suspension is added to the feed container of a prilling unit (Brace) and prilled at about 0.1 bar from a 200 µm nozzle. A periodic oscillation of the frequency of about 390 Hz is transmitted to the nozzle head in the course of this. The resulting drops are solidified in a cooling zone using air with a temperature of -30°C.

Example 15

30 g of tristearate, 60 g of solid paraffin, 4 g of sitosterol and 0.07 g of stearylamine are fused to give a clear mixture. The clear melt is cooled to 56-60°C. 15 g of pantoprazole sodium sesquihydrate are introduced and this is homogeneously dispersed. The suspension is prilled in the molten state in a prilling unit (Brace) having vibrating nozzles and the resulting drops are solidified in a cooling zone.

The preparations obtained according to Examples 1-15 have a particle size in the range 50-700 µm. By variation of the process conditions it is possible, for example, to obtain larger particles.

Preparation of the administration forms**Example A**

134.7 g of mannitol, 30 g of Kollidon® 30 and 20 g of xanthan are mixed in dry form. The mixture is granulated in a fluidized bed granulator using water. Granules having a particle size of 0.8-1.5 mm are obtained, which are mixed with the preparation (125 g) obtained according to Example 1. The mixture thus obtained is dispensed into sachets or compressed to give tablets – if desired together with further tablet excipients – in a manner known to the person skilled in the art.

Example B

An amount of the preparation obtained according to Example 2 corresponding to 22.6 mg of pantoprazole magnesium is mixed with 500 mg of lactose and 100 mg of xanthan. Depending on individual sense of taste, the mixture is additionally mixed with flavorings (sweetener, aroma) and then dispensed into a sachet. By dissolving the contents of a sachet in a glass of water with stirring, a suspension for oral administration is obtained.

Example C

An amount of the preparation from Example 3 corresponding to 45.2 mg of pantoprazole sodium sesquihydrate is mixed with the corresponding amount of lactose. This mixture is mixed with a mixture of citric acid and sodium carbonate. After addition of a suitable lubricant (e.g. sodium stearyl fumarate) and addition of one or more suitable flavorings, the mixture obtained is compressed directly (without further granulation) to give an effervescent tablet. By dissolving a tablet in a glass of water, a suspension for oral administration is obtained.

Example D

An amount of the preparation according to Example 4 corresponding to 45.2 mg of pantoprazole sodium sesquihydrate is mixed with lactose to improve the flow properties. The mixture is dispensed into hard gelatin capsules of suitable size together with other suitable active compounds (e.g. amoxicillin or NSAIDs in customary dose forms).

Example E

300 mg of lactose are added to an amount of the preparation according to Example 6 comprising 30 mg of lansoprazole. The two components are mixed with citric acid and sodium carbonate and, after addition of a suitable lubricant (e.g. sodium stearyl fumarate) and addition of suitable flavorings, compressed to give a tablet.

Example F

450 mg of sucrose and 300 mg of xanthan are added to an amount of the preparation according to Example 7 corresponding to 30 mg of rabeprazole. The components are mixed and treated with flavor corrigents. The granules are filled into sachets. The contents of a sachet can be added to a glass of water and, after stirring, are ready for use.

Example G

60 grams of the preparation according to Example 8 are mixed in dry form with 140 grams of mannitol, 30 grams of Kollidon 30 and 20 grams of xanthan. The mixture is granulated with water in a fluidized bed granulator. Granules are obtained with the particle size 0.8-1.5 mm. The mixture thus obtained is dispensed into sachets.

Patent claims

1. An administration form for acid-labile active compounds, comprising pharmaceutical excipients and multiple individual active compound units, wherein the acid-labile active compound is present in the individual active compound units in a matrix made of a mixture comprising at least one fatty alcohol and at least one solid paraffin.
2. An administration form for acid-labile active compounds, comprising pharmaceutical excipients and multiple individual active compound units, wherein the acid-labile active compound is present in the individual active compound units in a matrix made of a mixture comprising at least one triglyceride and at least one solid paraffin or in a matrix made of a mixture comprising at least one fatty acid ester and at least one solid paraffin.
3. The administration form as claimed in claim 1 or 2, wherein the individual active compound units are microspheres.
4. The administration form as claimed in claims 1 to 3, wherein the active compound present is an acid-labile proton pump inhibitor.
5. The administration form as claimed in claim 4, wherein the acid-labile proton pump inhibitor present is pantoprazole.
6. The administration form as claimed in claim 1 or 2, wherein, in the mixture, one or more further excipients, selected from the group consisting of polymers, sterols and basic compounds, is/are present in the individual active compound units.
7. The administration form as claimed in claim 6, wherein the polymer is selected from the group consisting of povidone, vinylpyrrolidone/vinyl acetate copolymer, polyvinyl acetate, cellulose ethers, cellulose esters, methacrylic acid/methyl methacrylate copolymer or methacrylic acid/ethyl methacrylate copolymer or wherein the polymer is mixtures thereof.
8. The administration form as claimed in claim 6, wherein the sterol is selected from the group consisting of ergosterol, stigmasterol, sitosterol, brassicasterol, campesterol, cholesterol and lanosterol or wherein the sterol is mixtures thereof.
9. The administration form as claimed in claim 6, wherein the basic compounds are inorganic basic salts such as ammonium carbonate and sodium carbonate, amines such as meglumine, di- or

triethylamine and TRIS (2-amino-2-hydroxymethyl-1,3-propandiol) or fatty amines such as stearylamine.

10. The administration form as claimed in claim 1 or 2, which consists of suspensions, gels, tablets, coated tablets, multicomponent tablets, effervescent tablets, rapidly disintegrating tablets, powders in sachets, sugar-coated tablets, capsules or suppositories.
11. An active compound unit comprising an acid-labile active compound, wherein the acid-labile active compound in the active compound unit is present in a matrix made of a mixture comprising at least one fatty alcohol and at least one solid paraffin.
12. An active compound unit comprising an acid-labile active compound, wherein the acid-labile active compound in the active compound unit is present in a matrix made of a mixture comprising at least one fatty acid ester and at least one solid paraffin or in a matrix made of a mixture comprising at least one triglyceride and at least one solid paraffin.
13. The active compound unit as claimed in claim 11 or 12, wherein one or more further excipients, selected from the group consisting of polymers, sterols and basic compounds, is/are present in the matrix.
14. The active compound unit as claimed in claims 11 to 13, wherein the active compound present is an acid-labile proton pump inhibitor.
15. The active compound unit as claimed in claims 11 to 14, which consists of a microsphere having a particle size range of 50-800 μm .
16. A process for the production of an active compound unit in the form of a microsphere comprising an acid-labile active compound, where the acid-labile active compound is present in the microsphere in a matrix comprising at least one fatty alcohol, by production of drops of a solution or dispersion of the acid-labile active compound in at least one fatty alcohol by means of vibrating nozzles and by solidification of the drops formed in a suitable medium.
17. A microsphere obtainable as claimed in claim 16.
18. A process for the production of an active compound unit in the form of a microsphere comprising an acid-labile active compound, where the acid-labile active compound is present in the microsphere in a matrix made of a mixture comprising at least one fatty alcohol and at least one solid paraffin, at least one triglyceride and at least one solid paraffin or at least one fatty acid

ester with at least one solid paraffin, comprising the following steps: (a) preparation of a solution or dispersion of the acid-labile active compound in the fatty alcohol and paraffin, triglyceride and paraffin or fatty acid ester and paraffin; (b) prilling of the liquid phase from (a); and (c) solidification of the drops formed in a suitable medium.

19. The process as claimed in claim 18, where the prilling is carried out by means of vibrating nozzles, the liquid phase flowing to the nozzle being kept at a constant temperature and the solidification of the drops taking place in a suitable cooling medium after stabilization thereof by sudden quenching.
20. A microsphere, obtainable by a process as claimed in claim 18 or 19.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

09/28/92

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference

(if desired) (12 characters maximum) B694WOORD0196706074

Box No. I TITLE OF INVENTION

Novel preparation and administration form comprising an acid-labile active compound

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

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This person is applicant for the purposes of:

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This person is:

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The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☐ agent

☒ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

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- ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	International application: receiving Office
item (1) (07.06.1999) 07 June 1999	99110865.5		EP	
item (2)				
item (3)				
<input type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s):				
* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.				
Box No. VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):		Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):		
ISA /		Date (day/month/year)	Number	Country (or regional Office)
		08 February 2000	EP 99110865	EP
Box No. VIII CHECK LIST; LANGUAGE OF FILING				
This international application contains the following number of sheets: request : 4 description (excluding sequence listing part) : 17 claims : 3 abstract : 1 drawings : sequence listing part of description : Total number of sheets : 25		This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input type="checkbox"/> other (specify):		
Figure of the drawings which should accompany the abstract:		Language of filing of the international application: EN		
Box No. IX SIGNATURE OF APPLICANT OR AGENT				
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).				
Byk Gulden Lomborg Chemische Fabrik GmbH		May 17, 2000 Date Dr. Rango DIETRICH		
i.V. Dr. Herbert Rupp i.V. Dr. Bernd Kratzer		17 May 2000 Date Dr. Rudolf LINDER		

For receiving Office use only	
1. Date of actual receipt of the purported international application: 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: 4. Date of timely receipt of the required corrections under PCT Article 11(2): 5. International Searching Authority (if two or more are competent): ISA /	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.	

For International Bureau use only
Date of receipt of the record copy by the International Bureau:
Form PCT/RO/101 (last sheet) (July 1998; reprint July 1999)

PATENT COOPERATION TREATY

Kr:

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

BYK GULDEN
Lomborg Chemische Fabrik GmbH
Byk-Gulden-Strasse
D-78467 Konstanz
ALLEMAGNE

EINGANG
RECEIVED
09. Feb. 2001
Gewerblicher
Rechtsschutz

Date of mailing (day/month/year) 02 February 2001 (02.02.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference B694WOORD0196706074	
International application No. PCT/EP00/04958	
International publication date (day/month/year) 14 December 2000 (14.12.00)	
Applicant BYK GULDEN et al	International filing date (day/month/year) 31 May 2000 (31.05.00) Priority date (day/month/year) 07 June 1999 (07.06.99)

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(a) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
07 June 1999 (07.06.99)	99110865.5	EP	07 Dec 2000 (07.12.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Anman QIU

Telephone No. (41-22) 338.83.38

So: LD✓
SR✓

PATENT COOPERATION TREATY

WO 00/74654
PCT/EP00/04958

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

BYK GULDEN
Lomborg Chemische Fabrik GmbH
Byk-Gulden-Strasse 2
D-78467 Konstanz
ALLEMAGNE

EINGANG
RECEIVED
27. Dez. 2000
Gewerblicher
Rechtsschutz

Date of mailing (day/month/year) 14 December 2000 (14.12.00)		
Applicant's or agent's file reference B694WOORD0196706074		IMPORTANT NOTICE
International application No. PCT/EP00/04958	International filing date (day/month/year) 31 May 2000 (31.05.00)	
Priority date (day/month/year) 07 June 1999 (07.06.99)		
Applicant BYK GULDEN et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AP,BA,BB,BG,BR,CA,CN,CR,CU,CZ,DM,EA,EE,EP,GD,GE,HR,HU,ID,IL,IN,IS,JP,LC,LK,
LR,LT,LV,MA,MG,MK,MN,MX,NO,NZ,OA,PL,RO,SG,SI,SK,TR,TT,UA,UZ,VN,YU,ZA

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
14 December 2000 (14.12.00) under No. WO 00/74654✓

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

BYK GULDEN

Lomborg Chemische Fabrik GmbH

Byk-Gulden-Strasse 2

D-78467 Konstanz

ALLEMAGNE

RECEIVED

09. Feb. 2001

Gewerblicher
Rechtsschutz

Date of mailing (day/month/year) 31 January 2001 (31.01.01)		
Applicant's or agent's file reference B694WOORD0136706074		IMPORTANT INFORMATION
International application No. PCT/EP00/04958	International filing date (day/month/year) 31 May 2000 (31.05.00)	
Priority date (day/month/year) 07 June 1999 (07.06.99)		
Applicant BYK GULDEN et al		

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

National : AU, BG, CA, CN, CZ, IL, JP, KP, KR, MN, NO, NZ, PL, RO, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

National : AE, AL, BA, BB, BR, CR, CU, DM, EE, GD, GE, HR, HU, ID, IN, IS, LC, LK, LR, LT, LV,

MA, MG, MK, MX, SG, SI, TR, TT, UA, UZ, VN, YU, ZA

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer S. Meila
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PCT

REC'D 03 AUG 2001

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference B694WOORD01	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/04958	International filing date (day/month/year) 31/05/2000	Priority date (day/month/year) 07/06/1999
International Patent Classification (IPC) or national classification and IPC A61K9/16		
Applicant BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH et al.		



1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 15/11/2000	Date of completion of this report 01.08.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer ESTANOL, I Telephone No. +49 89 2399 8647 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/04958

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-17 as originally filed

Claims, No.:

1-20 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/04958

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4-9,13,14,16,18-19
	No:	Claims	1,2,3,10-12,15,17,20
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations **see separate sheet**

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

1. Reference is made to the following documents:

- D1: L. LEWIS ET AL.: 'The physical and chemical stability of suspensions of sustained-release microspheres' JOURNAL OF MICROENCAPSULATION, vol. 15, no. 5, September 1998 (1998-09), pages 555-567, XP000771706 London (GB)
- D2: US-A-3 065 142 (ANTONIDES) 20 November 1962 (1962-11-20)
- D3: EP-A-0 208 971 (DR. KARL THOMAE GMBH) 21 January 1987 (1987-01-21)
- D4: DE 27 25 924 A (HOBEG) 21 December 1978 (1978-12-21) cited in the application

Suspensions of sustained release diclofenac (acid labile active compound) microspheres with a mean size of 137.3 μm comprising wax, glyceryl monostearate and stearyl alcohol are disclosed in D1 (pages 556 and 557). The microspheres obtained by the method disclosed in claims 16 or 18 or 19 cannot be distinguished from the microspheres disclosed in D1. Thus, the subject-matter of present claims 1, 2, 3, 10-12, 15, 17 and 20 is not new over D1 (Article 33(2) PCT).

D2 discloses a gastric preparation of pancreatin (acid labile active compound) in the form of granules or capsules or tablets comprising paraffin and glyceryl tristearate (column 3, lines 3-44, example 1). The preparation of D2 anticipates the active compound unit of present claim 12 and the administration form of present claims 2 and 10. The subject-matter of claims 2, 10 and 12 is therefore not new over D2 (Article 33(2) PCT).

The method of claims 16 or 18 or 19 is new over the cited prior art since D3 does not use an acid labile active compound.

2. The problem underlying the present invention may be regarded as how to provide an alternative administration form in which the acid labile active compound does not have to be protected by an enteric coating and a method of preparation.

D2 solves the same problem by providing a composition comprising an acid labile active compound (pancreatin) with paraffin and glyceryl tristearate. The selection of a

proton pump inhibitor such as pantoprazole as acid labile active compound (present claims 4-5) or the further incorporation in the composition such as polymers, sterols or basic compounds (present claims 6-9) can only be regarded as inventive, if it presents unexpected effects or properties in relation to the administration form of D2. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claims 4-9 and 13-14 (Article 33(3) PCT).

The subject-matter of claims 16, 18-19 does not involve an inventive step for the following reasons:

D2 solves the same problem by mixing the acid-labile active compound with a component being resistant to gastric disintegration, heating the mixture and solidifying the mixture. The difference between the method of D2 and the method of claims 16, 18 or 19 is that drops are produced from the mixture before solidification. This feature is described in D4 (page 12-17 and example 8) as providing the same advantages as in the present application. The skilled person would therefore regard it as a normal design procedure to include this feature in the method utilizing the preferred mixture for protecting the acid-labile active compound (paraffin and glyceryl tristearate) described in document D2 in order to solve the problem posed.

3. The subject-matter of claims 1 to 19 is applicable in the pharmaceutical industry (Article 33(4) PCT).

Re Item VIII

The embodiment of example 5 described on pages 13-14 does not fall within the scope of the claims since it does not comprise solid paraffine. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference B694WOORD01	<div style="display: flex; justify-content: space-between;"> <div> FOR FURTHER ACTION </div> <div> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) </div> </div>	
International application No. PCT/EP00/04958	International filing date (day/month/year) 31/05/2000	Priority date (day/month/year) 07/06/1999
International Patent Classification (IPC) or national classification and IPC A61K9/16		
Applicant BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		
Date of submission of the demand 15/11/2000	Date of completion of this report 01.08.2001	
Name and mailing address of the international preliminary examining authority: <div style="display: flex; align-items: center;"> <div> European Patent Office D-80288 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 </div> </div>	Authorized officer ESTANOL, I Telephone No. +49 89 2399 8647	



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/04958

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-17 as originally filed

Claims, No.:

1-20 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP00/04958**

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	4-9,13,14,16,18-19
	No: Claims	1,2,3,10-12,15,17,20
Inventive step (IS)	Yes: Claims	
	No: Claims	1-20
Industrial applicability (IA)	Yes: Claims	1-20
	No: Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/04958

Re Item V

1. Reference is made to the following documents:

- D1: L. LEWIS ET AL.: 'The physical and chemical stability of suspensions of sustained-release microspheres' JOURNAL OF MICROENCAPSULATION, vol. 15, no. 5, September 1998 (1998-09), pages 555-567, XP000771706 London (GB)
- D2: US-A-3 065 142 (ANTONIDES) 20 November 1962 (1962-11-20)
- D3: EP-A-0 208 971 (DR. KARL THOMAE GMBH) 21 January 1987 (1987-01-21)
- D4: DE 27 25 924 A (HOBEG) 21 December 1978 (1978-12-21) cited in the application

Suspensions of sustained release diclofenac (acid labile active compound) microspheres with a mean size of 137.3 μm comprising wax, glyceryl monostearate and stearyl alcohol are disclosed in D1 (pages 556 and 557). The microspheres obtained by the method disclosed in claims 16 or 18 or 19 cannot be distinguished from the microspheres disclosed in D1. Thus, the subject-matter of present claims 1, 2, 3, 10-12, 15, 17 and 20 is not new over D1 (Article 33(2) PCT).

D2 discloses a gastric preparation of pancreatin (acid labile active compound) in the form of granules or capsules or tablets comprising paraffin and glyceryl tristearate (column 3, lines 3-44, example 1). The preparation of D2 anticipates the active compound unit of present claim 12 and the administration form of present claims 2 and 10. The subject-matter of claims 2, 10 and 12 is therefore not new over D2 (Article 33(2) PCT).

The method of claims 16 or 18 or 19 is new over the cited prior art since D3 does not uses an acid labile active compound.

2. The problem underlying the present invention may be regarded as how to provide an alternative administration form in which the acid labile active compound does not have to be protected by an enteric coating and a method of preparation.

D2 solves the same problem by providing a composition comprising an acid labile active compound (pancreatin) with paraffin and glyceryl tristearate. The selection of a

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/04958

proton pump inhibitor such as pantoprazole as acid labile active compound (present claims 4-5) or the further incorporation in the composition such as polymers, sterols or basic compounds (present claims 6-9) can only be regarded as inventive, if it presents unexpected effects or properties in relation to the administration form of D2. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of claims 4-9 and 13-14 (Article 33(3) PCT).

The subject-matter of claims 16, 18-19 does not involve an inventive step for the following reasons:

D2 solves the same problem by mixing the acid-labile active compound with a component being resistant to gastric disintegration, heating the mixture and solidifying the mixture. The difference between the method of D2 and the method of claims 16, 18 or 19 is that drops are produced from the mixture before solidification. This feature is described in D4 (page 12-17 and example 8) as providing the same advantages as in the present application. The skilled person would therefore regard it as a normal design procedure to include this feature in the method utilizing the preferred mixture for protecting the acid-labile active compound (paraffin and glyceryl tristearate) described in document D2 in order to solve the problem posed.

3. The subject-matter of claims 1 to 19 is applicable in the pharmaceutical industry (Article 33(4) PCT).

Re Item VIII

The embodiment of example 5 described on pages 13-14 does not fall within the scope of the claims since it does not comprise solid paraffine. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference B694WOORD0196706074	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 00/ 04958	International filing date (day/month/year) 31/05/2000	(Earliest) Priority Date (day/month/year) 07/06/1999
Applicant BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/04958

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K31/4439

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 208 971 A (DR. KARL THOMAE GMBH) 21 January 1987 (1987-01-21) page 2, line 7 - line 11 page 18; example 8 ---	16-20
Y	DE 27 25 924 A (HOBEG) 21 December 1978 (1978-12-21) cited in the application page 12 -page 17; examples 1,2,5 ---	16-20
A	EP 0 351 580 A (SHIONOGI SEIYAKU KABUSHIKI KAISHA) 24 January 1990 (1990-01-24) page 4, column 6, line 11 - line 35 page 4, column 6, line 50 -page 5, column 7, line 7 page 7; example 7 --- -/--	1-20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

21 September 2000

Date of mailing of the international search report

28/09/2000

Name and mailing address of the ISA

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Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 00/04958

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 514 008 A (TAKEDA CHEMICAL INDUSTRIES) 19 November 1992 (1992-11-19) cited in the application page 6, line 31 - line 37 page 18; example 30 ----	1-20
A	DATABASE WPI Week 19952 Derwent Publications Ltd., London, GB; AN 1993-348343 XP002130012 & JP 05 255075 A (TAISHO PHARM CO LTD), 5 October 1993 (1993-10-05) abstract ----	1-20
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X	US 3 065 142 A (ANTONIDES) 20 November 1962 (1962-11-20) column 3; example 1 column 3, line 3 - line 5 ----	2, 10, 12
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A	US 3 800 038 A (RUDEL) 26 March 1974 (1974-03-26) column 6 -column 7; example 1 ----	6, 8, 13
A	FR 2 754 177 A (SANOFI SOCIÉTÉ ANONYME) 10 April 1998 (1998-04-10) page 17; example 10 page 13 -page 14; example 1 -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/04958

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/04958

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			PL 332249 A	30-08-1999
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(PCT Rule 61.2)

**Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE**
in its capacity as elected Office

Date of mailing (day/month/year) 31 January 2001 (31.01.01)	ETATS-UNIS D'AMERIQUE in its capacity as elected Office
International application No. PCT/EP00/04958	Applicant's or agent's file reference B694WOORD0196706074
International filing date (day/month/year) 31 May 2000 (31.05.00)	Priority date (day/month/year) 07 June 1999 (07.06.99)
Applicant DIETRICH, Rango et al	

- ☒ in the demand filed with the International Preliminary Examining Authority on: **15 November 2000 (15.11.00)**

- ☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer</p> <p>S. Mafla</p> <p>Telephone No.: (41-22) 338.83.38</p>
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PATENT COOPERATION TREATY

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DOCUMENT TRANSMITTED

From the INTERNATIONAL BUREAU

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United States Patent and Trademark
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Arlington, VA 22202
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in its capacity as designated Office

Date of mailing (day/month/year)

02 February 2001 (02.02.01)

International application No.

PCT/EP00/04958

International filing date (day/month/year)

31 May 2000 (31.05.00)

Applicant

BYK GULDEN et al

The International Bureau transmits herewith the following documents and number thereof:

_____ cop(ies) of priority document(s) (Rule 17.2(a))

The International Bureau of WIPO
34, chemin des Colombettes
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PATENT COOPERATION TREATY

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From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

BYK GULDEN
Lomborg Chemische Fabrik GmbH
Byk-Gulden-Strasse 2
D-78467 Konstanz
ALLEMAGNE

Date of mailing (day/month/year) 02 February 2001 (02.02.01)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference B694WOORD0196706074	
International application No. PCT/EP00/04958	International filing date (day/month/year) 31 May 2000 (31.05.00)
International publication date (day/month/year) 14 December 2000 (14.12.00)	Priority date (day/month/year) 07 June 1999 (07.06.99)
Applicant BYK GULDEN et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
07 June 1999 (07.06.99)	99110865.5	EP	07 Dec 2000 (07.12.00)

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1211 Geneva 20, Switzerland

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